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Abstract: BACKGROUND: Growth impairment remains a major concern in children with Crohn's disease, but evidence remains unclear, in particular, whether steroid use is implicated. We aimed to (1) determine the frequency of temporary (TGI) and permanent (PGI) growth impairment in children administered steroids and (2) examine whether cumulative steroid administration was associated with TGI and/or PGI. METHODS: A retrospective cohort study was performed in patients with Crohn's disease (<18 yr) administered steroids at the gastroenterology clinics of Sainte-Justine Hospital, Montreal. Steroid dosage, height during follow-up, adult height (after age 20), and parental heights were ascertained. Patients with height z score <-1.64 on more than 1 occasion before age 18 were considered as patients with TGI. Patients with adult heights <8.5 cm below the expected target heights were considered as patients with PGI. Association between steroid dosage and TGI/PGI was studied using logistic regression analyses. Data from the Swiss IBD Cohort Study were analyzed for comparison. RESULTS: A total of 221 children were studied. Approximately 19% (42/221) children were deemed as TGI, and 8/137 patients (5.8%) had PGI. TGI was associated with diagnosis at younger age (P value 0.002) and steroid administration at younger age (P value 0.001), but not with steroid dosage. Final adult height was associated with target height, but not with cumulative steroid dosage. Rates of PGI in the Swiss cohort were 9.1% in steroid users and 2.7% in nonusers. CONCLUSIONS: Most children with TGI attain normal adult heights. Cumulative steroid use does not seem to be associated with either TGI or PGI in children with Crohn's disease.

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Steroid Administration and Growth Impairment in Children with Crohn's Disease

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Background: Growth impairment remains a major concern in children with Crohn's disease, but evidence remains unclear, in particular, whether steroid use is implicated. We aimed to (1) determine the frequency of temporary (TGI) and permanent (PGI) growth impairment in children administered steroids and (2) examine whether cumulative steroid administration was associated with TGI and/or PGI.

Methods: A retrospective cohort study was performed in patients with Crohn's disease (<18 yr) administered steroids at the gastroenterology clinics of Sainte-Justine Hospital, Montreal. Steroid dosage, height during follow-up, adult height (after age 20), and parental heights were ascertained. Patients with height z score <-1.64 on more than 1 occasion before age 18 were considered as patients with TGI. Patients with adult heights <8.5 cm below the expected target heights were considered as patients with PGI. Association between steroid dosage and TGI/PGI was studied using logistic regression analyses. Data from the Swiss IBD Cohort Study were analyzed for comparison.

Results: A total of 221 children were studied. Approximately 19% (42/221) children were deemed as TGI, and 8/137 patients (5.8%) had PGI. TGI was associated with diagnosis at younger age (*P* value 0.002) and steroid administration at younger age (*P* value 0.001), but not with steroid dosage. Final adult height was associated with target height, but not with cumulative steroid dosage. Rates of PGI in the Swiss cohort were ~9.1% in steroid users and 2.7% in nonusers.

Conclusions: Most children with TGI attain normal adult heights. Cumulative steroid use does not seem to be associated with either TGI or PGI in children with Crohn's disease.

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Key Words: growth impairment, Crohn's disease, corticosteroids, adult height

Growth impairment is a major clinical challenge in children diagnosed with Crohn's disease (CD). Rates of up to 80% have been reported.[1–3] In many children, growth impairment precedes the diagnosis of disease. Whether this impairment is related to the disease process itself or to other unknown risk factors is currently unclear. In a number of children, however, growth impairment develops during the disease course. This impairment is suggested to be due to a complex interplay between nutritional-, inflammation-, hormonal-, and treatment-related factors. A key question is, however, whether growth impairment observed during the disease process leads to failure to achieve normal adult height. Evidence regarding the occurrence of permanent growth impairment (PGI) is, however, currently inconsistent. Although some studies indicate that PGI is common,[4,5] others suggest otherwise.[6–8] Disease heterogeneity, variability in measures used to classify the growth impairment phenotype, and lack of accounting for genetic effects on growth may have resulted in these discrepant results. In this context, recently, using parental heights, Lee et al[9] showed that indeed the final adult heights of children with CD are strongly related to parental heights and that only ~11% of children had persistent growth impairment or PGI in adulthood. This study highlights the importance of an appropriate classification of the growth impairment phenotype in children with CD.

Steroids are the mainstay in the treatment of CD in children. Numerous studies have demonstrated that steroid use can influence linear growth in children.[7] These effects are believed to be mediated through the growth hormone–insulin factor 1 axis.[3,10] Although there is considerable biological data, epidemiological evidence of the impact of steroid use and growth impairment in children with CD remains limited and controversial. Although some studies suggest a detrimental effect on growth,[5,8]

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others do not support this relationship.[9] Furthermore, some studies have shown that although steroid use may result in temporary growth impairment (TGI), many children demonstrate catch-up growth such that their final adult heights are within reference ranges.[6,8,11] The major limitation of previous studies is the lack of comprehensive data on steroid use and the inability to adjust for other potential risk factors (disease activity, for example) that could influence growth independently of steroid usage. To further clarify the role of steroids in TGI and PGI, we performed a detailed study on a cohort of children who were administered steroids and in who we used parental heights to define the PGI phenotype.

METHODS

This study was based on a recent retrospective cohort study that investigated the burden and predictors of steroid resistance and dependence in children with CD.[12] It was performed at the gastroenterology clinic of Sainte-Justine Hospital (SJH), Montreal. Patients were children <18 years of age diagnosed with CD using standard clinical, histological, radiological, and endoscopic criteria.[13,14] The medical records of these children diagnosed between the years 1980 and 2007 were retrospectively reviewed to identify patients who received corticosteroids since diagnosis. Clinical details, such as disease characteristics (location and behavior) at diagnosis, corticosteroid therapy, concomitant medication, extraintestinal manifestations, surgeries, and family history of inflammatory bowel disease (IBD), were abstracted. Pubertal stage was not available for most patients. Boys below the age of 13 and girls below the age or 11 were considered prepubertal. Information on racial and ethnic background was acquired by administering a supplementary questionnaire. CD was classified according to the World Gastroenterology Organization's Montreal classification.[15] Concomitant medication for the purpose of this study was considered if it was introduced during initial corticosteroid therapy before the start of corticosteroid tapering and not if it was given in response to disease relapse. Disease severity was assessed using a modified Harvey–Bradshaw index.[16] The only modification made to the original index was that the average number of stools during a 24-hour period was assigned scores as follows: none = 0; 1 to 2 = 1; 3 to 4 = 2; 5 to 7 = 3; 8 to 9 = 4; ≥10 = 5.

For corticosteroid use, we abstracted data on the following:

1. Age at which steroids were first introduced
2. Dose of steroid administered (milligram/day using recorded weights)
3. Duration (days)
4. Modifications of dosage if any
5. Number of steroid courses
6. Type of steroid
7. Mode of delivery (oral or injection).

At the study center, the usual practice was a starting dose of intravenous or oral prednisone at 1 mg/kg per day for 2 to 4 weeks. Dosages are tapered within 8 to 12 weeks depending on patient response comprising usually of prednisone dosage reduction of 5 mg/wk. The starting dose for budesonide was usually 9 mg/d, tapering with decrements of 3 mg over the course of 3 to 4 weeks. Using the dosage information and the duration of treatment, we estimated the cumulative dosage of steroids for each patient (dosage × duration for all episodes of steroid use throughout the duration of the study interval). When corticosteroids other than prednisone were administered (hydrocortisone, methylprednisolone), we used reported conversion tables to convert all steroids to prednisone with the exception of budesonide.[17] For the purpose of our study, we considered budesonide in a 1:1 ratio compared with prednisone.

We abstracted steroid data both from the gastroenterology clinic and any other department that the child may have visited (e.g., the emergency department resulting from a disease flare). For some patients, steroid dosage modifications were made over phone by the consulting gastroenterologist. We abstracted such dosage modifications as well. Similar information was collected for all steroid courses.

Assessment of Growth Impairment

Temporary Impairment

For each visit of the child, we abstracted the date of visit and recorded height (centimeter) before disease diagnosis (where available) at the time of disease diagnosis, before and subsequent to steroid commencement, till the last reported visit. Based on this information, we estimated the height of each individual at different ages. Height z scores were than estimated using the WHO 2007 reference values[18] for each age separately for gender. Z-scores <-1.64 (corresponding to the fifth percentile of the reference population height distribution) were used as the cutoff. To compare results with previous studies,[9,19,20] a z score of <-1.64 on more than 1 measurement was required for classification to the growth impairment phenotype.

Permanent Impairment

All patients who had completed 19 years of age at the time of the start of the study (2011) were contacted to acquire their final adult height. Similarly, their parents were contacted to acquire their heights. The target height for the patient was estimated as follows:

For boys: {paternal height (centimeter) + (maternal height [centimeter] +13)}/2;

For girls: {paternal height (centimeter) + (maternal height [centimeter] −13)}/2.

Patients with adult heights 8.5 cm below the target height were considered as not having achieved their expected adult heights and deemed permanently growth impaired.[21]

To compare findings related to adult height from our study to those within steroid users and nonusers of an independent population, we analyzed data from a recent study[22] that was based on the Swiss IBD Cohort Study. Data from this study were acquired on the subset of individuals who were diagnosed with

CD during childhood (<18 yr of age). Data on gender, age at diagnosis, whether administered steroids or not, age when final height was measured, and final adult height measures (centimeter) were acquired. We included only those patients whose final adult height was measured after age 19. To estimate final adult height z scores, we used the data provided by the Swiss Federal Office of Public Health Survey of 2007.[23] Parental heights were, however, not available for this study.

The institutional ethical board approved the study and consent was acquired from the patients.

Statistical Analyses

Analysis was restricted to growth impairment that occurred subsequent to steroid administration. Thus, all patients who had height z scores <1.64 on more than 1 occasion before the date of administration of steroids were excluded from the study. For the eligible children, the frequency of TGI and PGI along with their 95% confidence intervals (CIs) was estimated assuming a binomial distribution. Univariate analyses included comparing the distribution of relevant clinical and socio-demographic variables between growth impaired and nonimpaired children. For continuous variables, such as age at diagnosis, age at steroid administration, and cumulative steroid dose, tertiles were created using the entire cohort. Single variable unconditional logistic regression models were fit to estimate the univariate associations. To examine multivariate associations, variables that seemed associated with TGI in the univariate analysis (P values < 0.10) were entered a logistic regression model. Potential multicollinearity between variables was gauged by estimating variance inflation factors using the "collin" command in STATA (Stata Statistical Software: Release 10.1.; StataCorp, College Station, TX). Odds ratios (OR) and 95% CI were estimated.

To examine the predictors of final adult height, a linear regression model was fit to the data. Both univariate and multivariate regression analyses was performed. Beta coefficients (along with their 95% CI) and P values were estimated for each predictor.

To assess temporal trends in growth impairment, a stratified analysis was performed with stratification coinciding with the change in CD management over time (increasing use of immune-modulators and introduction of anti–tumor necrosis factor [TNF] medication era, year 2000).

RESULTS

A total of 237 patients were studied. From these, 13 (5.5%) had growth impairment before the administration of steroids, leaving 224 patients for further analysis. Another 3 patients who received steroids after the age of 18 were also excluded. The final analysis was based on 221 patients. The mean (±SD) age at diagnosis was 12.4 (±3.25) years (Table 1). The mean (±SD) age at start of steroids was 12.7 (±3.2) years. The mean (±SD) duration of follow-up since diagnosis was 1796 (±1048.6) days. There were more males (54.3%), and most patients were pubertal (62.9%). The median (range) steroid dosage was 3697.5 mg (350–51,757). Most patients had ileocolonic disease (60.2%) with the inflammatory phenotype (89.1%). Disease severity according to Harvey–Bradshaw index was mild–moderate in 57.5% of patients. Most patients were administrated concomitant medications with approximately 10% patients diagnosed before year 2000 administered immune-modulators as compared with 50% among those diagnosed subsequent to year 2000. Anti-TNF medication was administered to 16 (7.2%) of the patients. Fifteen of these children were diagnosed after year 2000. Family history of IBD (first-degree relatives) was reported in 10.4% of patients. Most patients were of white ancestry (93.7%).

Approximately 19.0% (95% CI, 13–24) of the children (42/221) had height z score of <-1.64 on >1 height measure. Thus, the frequency was ~4 times greater than expected (5% of normal and otherwise healthy children will have heights for age/gender that are 1.64 SDs below the mean). Univariate analysis (Table 2) suggested that early age at disease diagnosis (<11.6 yr versus >14 yr; OR, 7.5; 95% CI, 2.1–26.7; P value 0.002) and early age at steroid administration (<11.6 yr versus >15.9 yr; OR, 6.8; 95% CI, 2.2–21.1; P value 0.001) were associated with increased risk for TGI. There were suggestions that children who were prepubertal were more likely to be growth impaired (OR, 1.71; 95% CI, 0.87–3.38), but this association was not statistically significant (P value = 0.12). There were suggestions that increasing cumulative dose of steroids was associated with increasing risk for growth impairment (highest tertile versus lowest; OR, 1.6; 95% CI, 0.7–3.8); however, no clear trends were observed (P value for trend >0.05). Patients who had concomitant or disease limited only to the upper tract had slightly higher rates of growth impairment (21.3%) compared with those without (18.1%), but these differences were not statistically significant. No other clinical or socio-demographic variable seemed to be associated with growth impairment. Stratification on the year of diagnosis (before and after 2000), the rates of TGI were higher in the pre-2000 era (25.2% versus 14.9%). These differences correspond with an increasing use of immune-modulators in the post-2000 era (10% versus 50%). In multivariate analysis (Table 3), associations only with age at steroid start were evident. Compared to children who were administered steroids after age 14, children administered steroids earlier (<11.6 yr; OR, 5.4; 95% CI, 1.7–17.1; P value 0.004 and 11.8–14 yr; OR, 6.9; 95% CI, 2.2–21.6; P value 0.001) were significantly at higher risks for growth impairment. There was no evidence of multicollinearity (variance inflation factor ~5.0) between cumulative steroid dosage and age at steroid start.

For 137 children, information on final adult height and parental height was available. Of these, 8 patients (5.8%; 95% CI, 1.8–9.8) achieved adult heights that were 8.5 cm below that of their target height. This rate amounted to a frequency that was almost 2 times than the expected rate (3% of normal and otherwise healthy individuals are expected to have adult heights that are <8.5 cm below their target heights). Using final height z scores, 7.3% of the patients (95% CI, 2.9–11.7) were below the cutoff value (<-1.64), suggesting a growth impairment rate

TABLE 1. Characteristics of the Montreal Study Population (N = 221)

Characteristic	Number (%)
Age at diagnosis (mean ± SD)	12.4 (3.25)
Age at diagnosis	
Tertile 1 (2–11.6 yr)	75 (33.9)
Tertile 2 (11.8–14 yr)	81 (36.6)
Tertile 3 (14.6–18 yr)	65 (29.4)
Age at steroid start (mean ± SD)	12.7 (3.2)
Age at steroid start	
Tertile 1 (2.7–11.6 yr)	74 (33.4)
Tertile 2 (13.1–14.5 yr)	74 (33.5)
Tertile 3 (15.9–17.8 yr)	73 (33.0)
Gender	
Male	120 (54.3)
Female	101 (45.7)
Puberty	
Prepubertal	82 (37.1)
Pubertal	139 (62.9)
Steroid dose (median, range)	3697.5 (350–51,757)
Steroid dose	
Tertile 1 (350–2660 mg)	70 (31.7)
Tertile 2 (2670–5177.5 mg)	75 (33.9)
Tertile 3 (5180–51,757 mg)	76 (34.4)
Disease behavior[a]	
Inflammatory (±*P*)	197 (89.1)
Stricturing/penetrating (±*P*)	24 (10.9)
Disease location[a]	
Ileal only	15 (6.8)
Ileal (±L4)	11 (5.0)
Colonic only	47 (21.3)
Colonic (±L4)	12 (5.4)
Ileocolonic only	98 (44.3)
Ileocolonic (±L4)	35 (15.8)
L4 only	3 (1.4)
Concomitant medications[b]	
Before 2000	
None	13 (14.3)
Immuno-modulators	9 (9.9)
5-aminosalicylic acid	69 (75.8)
After 2000	
None	11 (9.7)
Immuno-modulators	58 (50.9)
5-aminosalicylic acid	45 (39.5)
Anti-TNF medication	
No	205 (92.8)
Yes	16 (7.2)
Surgery	
No	212 (95.9)
Yes	9 (4.1)
Disease activity[c]	
Mild–moderate	127 (57.5)
Severe	94 (42.5)
Family history of IBD[d]	
No	198 (89.6)
Yes	23 (10.4)
Ethnicity	
Non-white	14 (6.3)
White	207 (93.7)

[a]Disease behavior and location classified according to the World Gastroenterology Organization's Montreal Classification, L4, upper tract.
[b]Concomitant medications administered at the initiation of steroid therapy.
[c]Based on the modified Harvey–Bradshaw index.
[d]IBD in first-degree relative.

that was ~1.5 greater than expected (5% or normal children are expected to have heights below the cutoff of −1.64 SD). On univariate analysis, gender, puberty, and target height were associated with final adult height (Table 4). No associations between increasing steroid dosage and final adult height were evident. On multivariate analysis, only target height was associated with final adult height (Table 4). For the Swiss cohort, 119 subjects were eligible for analysis, of which 44 (37%) were administered steroids and 75 (63.0%) had not been administered steroids. Based on final adult height z scores, 4 patients (9.1%; 95% CI, 3.4–21.1) among those who were administered steroids and 2 patients (2.7%; 95% CI, 0.7–9.2) among those who had never been administered steroids had z scores below the cutoff. After accounting for normal expectations, the rate of growth impairment was ~2 times higher among steroid users, whereas there was no evidence for PGI among steroid nonusers.

DISCUSSION

In a well-characterized cohort of pediatric patients with CD administered corticosteroids, we observed that approximately 19% of children were at risk for TGI and between 5.8% (based on expected target height) and 7.3% (based only on final adult heights) of children were at risk for PGI. In the Swiss IBD cohort, 9.1% of steroid users and 2.7% were deemed as permanently growth impaired based on final adult height measures, not accounting for parental heights. These findings indicate that most patients with TGI attain their target final adult heights, that the burden of PGI from steroid usage is higher than nonsteroid users, and that the rates of PGI are ~1.5 to 2 times higher than those expected in the normal population.

Administration of steroids at an early age was associated with temporary impairment. Increasing steroid doses was, however,

TABLE 2. Association Between Temporary Growth Impairment and Socio-demographic and Clinical Characteristics in the Montreal Cohort: Univariate Analysis

Characteristic	Growth Impaired, N (%)	Normal Growth, N (%)	Odds Ratio (95% CI)	*P*
Age at diagnosis (tertiles)				
T3	3 (7.1)	62 (34.6)	Reference	
T2	19 (45.2)	62 (34.6)	6.3 (1.8–22.5)	0.004
T1	20 (47.6)	55 (30.7)	7.5 (2.1–26.7)	0.002
Age at steroid start (tertiles)				
T3	4 (9.5)	69 (38.6)	Reference	
T2	17 (40.5)	57 (31.8)	5.1 (1.6–16.1)	0.005
T1	21 (50.0)	53 (29.6)	6.8 (2.2–21.1)	0.001
Gender				
Female	19 (45.2)	82 (45.8)	Reference	
Male	23 (54.8)	97 (54.2)	1.0 (0.52–2.0)	0.95
Puberty				
Pubertal	22 (52.4)	117 (65.4)	Reference	
Prepubertal	20 (47.6)	62 (34.6)	1.71 (0.87–3.38)	0.12
Steroid dose (tertiles)				
T1	10 (23.8)	60 (33.5)	Reference	
T2	16 (38.1)	59 (33.0)	1.6 (0.7–3.9)	0.27
T3	16 (38.1)	60 (33.5)	1.6 (0.7–3.8)	0.29
Disease behavior				
Inflammatory	39 (92.9)	158 (88.2)	Reference	
Noninflammatory	3 (7.1)	21 (11.7)	1.7 (0.5–6.1)	0.40
Disease location				
Ileal	6 (14.3)	23 (12.8)	Reference	
Colonic	10 (23.8)	49 (27.4)	0.8 (0.3–2.4)	0.67
Ileocolonic	26 (61.9)	107 (59.8)	0.9 (0.3–2.5)	0.89
Upper tract[a]				
No	29 (18.1)	131 (81.9)		
Yes	13 (21.3)	48 (78.7)	1.22 (0.59–2.54)	0.59
Concomitant medications				
No	7 (16.7)	18 (10.1)	Reference	
Yes	35 (83.3)	161 (89.9)	0.6 (0.2–1.4)	0.23
Surgery				
No	41 (97.6)	171 (95.5)	Reference	
Yes	1 (2.4)	8 (4.5)	0.5 (0.1–4.3)	0.55
Disease activity				
Mild–moderate	23 (54.8)	104 (58.1)	Reference	
Severe	19 (45.2)	77 (41.9)	1.1 (0.6–2.3)	0.69
Family history				
No	36 (85.7)	162 (90.5)	Reference	
Yes	6 (14.3)	17 (9.5)	1.6 (0.6–4.3)	0.36
Ethnicity				
Non-white	2 (4.8)	12 (6.7)	Reference	
White	40 (95.2)	167 (93.3)	1.4 (0.3–6.7)	0.64

[a]Includes patients who had disease limited to the upper tract only or in combination with other sites.

TABLE 3. Association Between Temporary Growth Impairment and Socio-demographic and Clinical Characteristics in the Montreal Cohort: Multivariate Logistic Regression Analysis

Characteristic	Odds Ratio (95% CI)	*P*
Age at steroid start		
T3	Reference	
T2	5.4 (1.7–17.1)	0.004
T1	6.9 (2.2–21.6)	0.001
Steroid dose		
T1	Reference	
T2	1.7 (0.7–4.2)	0.24
T3	1.3 (0.5–3.2)	0.56

not associated with temporary impairment. Most patients with temporary impairment demonstrated catch-up growth and attained their target adult height. Final adult heights of the patients were associated with target heights, but not with steroid dosage.

Corticosteroids are the mainstay of therapy for pediatric-onset CD. It could thus be surmised that long-term steroid administration to children diagnosed with CD may hamper growth. The growth-suppressive effects of corticosteroids are believed to occur at different steps during the linear growth process and intimately related to the growth hormone–insulin factor 1 axis. Steroids impair the pulsatile release of growth hormone altering its output.[24,25] In addition, they reduce growth hormone receptor expression, hepatic growth hormone receptor binding, growth hormone receptor mRNA levels, and plasma levels of growth hormone-binding protein in a dose-dependent fashion.[26] Similarly, the activity of insulin growth factor 1 falls within hours of steroid administration.[27] This decreased activity is related to a concurrent increase in the insulin growth factor binding protein 3 protein levels suggesting that steroid administration reduces the bioavailability of insulin growth factor 1.[28,29] This in turn can lead to reduced proliferation of chondrocytes and delayed epiphyseal maturation, leading to growth suppression.

Although a biological link between steroids and growth impairment is known,[30] it is unclear whether steroids administration in children with CD impairs growth. For example, in a prospective study in 69 children with IBD, Motil et al[6] serially monitored height for 3 years. Steroid therapy was recorded at the time of entry into the study. Although there were deficits in linear growth, these deficits were found to be associated with disease activity but not with steroid therapy. These findings were supported by 2 subsequent studies. Sentongo et al[31] in a study based on 132 children with CD reported no association between lifetime steroid exposure and growth impairment in their cohort. Similarly, Wine et al[32] in a cohort of 93 patients with CD reported associations of growth impairment with disease severity but not with steroid therapy. Similarly, Lee et al[9] in a prospective study did not observe any association between steroid use and growth impairment. In contrast to these findings, Markowitz et al[5] observed that children with CD and PGI were administered steroids for a longer duration. Alemzadeh et al[8] reported that steroid use during puberty was associated with a lower adult height. In a recent prospective study, Pfefferkorn et al[19] (n = 176) reported that corticosteroid use for greater than 6 months in the first year was associated with abnormal height velocity at 1 year after adjusting for disease severity. At 2 years, however, those with sustained use of corticosteroids during the first year, but discontinuation in year 2, showed improvements in height velocities at year 2. As the adult heights were not ascertained, it was not clear whether corticosteroid use was associated with permanent effects on growth in this study.

Our study provides further support for a lack of association between cumulative steroid use and growth impairment. The rates of temporary impairment (19%) are similar to those reported recently by Lee et al (21%)[9] in their prospective study. Interestingly, ~90% of their cohort was administered steroids. Although they did not evaluate detailed steroid usage, in their study, children who used steroids were not found to be more likely to be growth impaired (temporary) and steroid use was not associated with final adult height. The rates of PGI (based on final adult height) were also comparable (7.3% in the Montreal cohort and 9.1% in the Swiss cohort) with those reported by Lee et al[9] (11.3%). Rates of PGI estimated in the Montreal cohort (5.8%) could not be compared as they could not be estimated in the Swiss cohort and were not reported in the study of Lee et al.[9]

It is interesting to note that the rates of growth impairment (in particular PGI) we observed were considerably lower than those reported in CD cohorts examined in the 1990s and early 2000. Treatment of patients with CD had evolved considerably during the last decade with the addition of immuno-modulators and anti-TNF antibodies. These treatments are likely to have modified the growth phenotype and contributed to the lower frequencies currently observed. Toward this end, TNF-α antibodies have been shown to promote growth in children with CD diagnosed with TGI.[33] Approximately 7% of our cohort was administered biologics and comprised mostly patients diagnosed after year 2000, and this may have contributed to the low rates of growth impairment observed. Similarly, the use of immune-modulators has dramatically increased subsequent to year 2000 and could have contributed as well. It is nonetheless important to note that the rates of PGI observed in our Montreal and Swiss steroid cohorts were ~2 times higher than those expected in normal individuals. Furthermore, in the Swiss cohort of nonsteroid users, there was no evidence of an increase in rates above those normally expected. This would suggest that patients who are administered steroids are at greater risk for PGI (as compared to those not administered steroids and the normal population), but this does not seem to be related to cumulative steroid usage. Although the lack of variability in disease activity may have precluded adequate exploration of the link between disease activity and growth impairment in our Montreal cohort, overall steroids are mainly prescribed to children with moderate–severe disease

TABLE 4. Association Between Final Adult Height and Clinical and Demographic Characteristics in the Montreal Cohort (Univariate and Multivariate[a] Linear Regression Analyses)

Characteristic	Univariate β-coefficient (95% CI)	*P*	Multivariate β-coefficient (95% CI)	*P*
Age at diagnosis (tertiles)				
T3	Reference			
T2	2.53 (−1.18 to 6.25)	0.18		
T1	3.35 (−0.48 to 7.19)	0.09		
Age at steroid start (tertiles)				
T3	Reference			
T2	1.41 (−2.27 to 5.09)	0.45		
T1	2.41 (−1.37 to 6.18)	0.21		
Gender				
Female	Reference			
Male	12.74 (10.5 to 15.0)	<0.001	2.37 (−0.37 to 5.10)	0.09
Puberty				
Pubertal	Reference			
Prepubertal	−3.87 (−7.04 to −0.69)	0.018	−0.58 (−2.46 to 1.30)	0.54
Steroid dose (tertiles)				
T1	Reference			
T2	−0.36 (−4.23 to 3.50)	0.85	0.22 (−1.90 to 2.33)	0.84
T3	0.81 (−3.01 to 4.64)	0.67	0.76 (−1.39 to 2.91)	0.49
Disease behavior				
Inflammatory	Reference			
Noninflammatory	3.58 (−1.06 to 8.22)	0.13		
Disease location				
Ileal	Reference			
Colonic	−2.85 (−8.21 to 2.51)	0.29		
Ileocolonic	−2.24 (−7.03 to 2.55)	0.36		
Concomitant medications				
No	Reference			
Yes	−0.40 (−4.86 to 4.06)	0.86		
Surgery				
No	Reference			
Yes	−5.06 (−11.58 to 1.46)	0.13		
Disease activity				
Mild–moderate	Reference			
Severe	−0.37 (−3.48 to 2.73)	0.81		
Family history				
No	Reference			
Yes	−1.10 (−6.36 to 4.16)	0.68		
Ethnicity				
Non-white	Reference			
White	1.97 (−8.56 to 12.50)	0.71		
Target height	0.89 (0.79 to 0.99)	<0.001	0.79 (0.63 to 0.96)	<0.001

[a]Only characteristics that are statistically significant (*P* value < 0.05) were included in the multivariate analysis, which also included the steroid dosage variable.

activity and thus disease activity per se rather than steroid use may be related to PGI. The latter is supported by the observed non-increase in rates of PGI in the Swiss cohort of children not administered with steroids. By and large, such patients have milder disease activity and hence do not necessitate the administration of steroids. These observations remain speculative at this time and require further clarification through additional, in particular, longitudinal data.

The retrospective nature of our study may have introduced bias, in particular, in the ascertainment of the height measures. To avoid misclassification, only children with >1 height z score <1.64 during follow-up were classified as temporarily growth impaired. Adult height was directly acquired from the patients and their parents. Although based on self-report, we do not anticipate major misclassification as height measures based on self-report have been shown to be reliable.[8,34–36] Height velocity measures may be more representative of temporal growth changes, but the retrospective nature of our study made ascertaining them for all patients difficult. To our knowledge, there are no dosage conversions for budesonide to prednisone. We considered their doses to be equivalent. This strategy may have led to potential misclassification in total steroid dosage. However, analyses of the data after excluding doses of budesonide did not reveal any differences (data not shown). We thus believe that considering budesonide to be equivalent to prednisone did not influence the final results. Sawczenko et al[37] based on height measures at diagnosis previously reported that the mean height z scores were significantly (*P* value <0.05) lower in children with jejunal (−0.9) and esophageal (−0.6) disease. The relationship between height and jejunal disease, however, did not maintain significance when the delay to diagnosis was accounted for in a regression analysis. As we used the Montreal classification, we were unable to study associations specifically between growth impairment and proximal small bowel disease. We, however, did examine associations between diseases involving the upper gastrointestinal tract (that included the jejunum and esophagus) either in isolation or in combination with other sites and did not find any association either with TGI or with PGI. Certainly, these associations need further investigation.

In conclusion, our study suggests that current treatment modalities for CD in children have resulted in lowering the frequency of, in particular, PGI even among those administered steroids. Nonetheless, rates are much higher in steroid users as compared with nonusers. Keeping in mind the other consequences of long-term steroid usage in children with CD, its judicious usage in the appropriate management of the disease is warranted.

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